

Remarks

Claims 1-3, 17-19, 21 and 25 are pending. Claims 1-3, 17-19, 21 and 25 are rejected. Claims 1 and 18 have been amended to change C₁₋₂₂ alkyl to C₁₋₁₀ alkyl in subparagraph (b). No new matter has been added.

Claim Rejections under 35 U.S.C. §103(a)

The Office Action rejects claims 1-3, 17-19, 21 and 25 under 35 U.S.C. §103(a), as allegedly unpatentable over Simpkins *et al.* (US 5,972,923) in view of Snow *et al.* (US 6,939,570).

1. Teachings of Simpkins *et al* as cited in the Office Action

Claims 1-3, 17-19, 21 and 25 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Simpkins *et al.* The office action alleges that the substitution of one polyphenol, flavanoid for another within the same genus would have been obvious to a person skilled in the art.

Simpkins teaches specifically that the cryoprotective effects of a polycyclic phenol is substantially enhanced when administered in combination with at least one additional anti-oxidant (column 3, lines 49-52). An example of such a cryoprotectant is the combination of

- (i) a **polycyclic phenol**, in this case estrogens or estradiols, **and**
- (ii) an **anti-oxidant** selected from: (a) thiols (R-S-H), (b) phenols, (c) spin trapping agents, (d) aromatic amines, (e) carotenoids, (f) flavonoids, and (g) ubiquinones.

At column 5, lines 1-12, a list is provided which includes specific examples of anti-oxidants from each of the categories (a) – (g).

Specifically the phenol examples (lines 1-5) include the following ten compounds: probucol, salicylates, Trolox C, 3,4-dihydroxytoluene; 3,4-dihydroxycinnamic acid; nordihydroxyquaiarectic acid; 2", 4'-dihydroxyacetophenone; 2',5'-dihydroxyacetophenone; 3'4'-dihydroxyacetophenone, and propylgallate

Specifically the flavonoids examples (lines 10-12) include the following eight compounds: (+)catechin, dihydroquercetin, hesperetin, taxasin, biochanin A, kaempferol, quercetin and 6,7-dihydroxy-4'-methoxy-isoflavanol.

At column 5, lines 30-44 Simpkins speculates:

The combination of anti-oxidant and polycyclic phenolic compounds including estrogens has utility in protecting cells from damage resulting from any of a number

of events that are known to be detrimental to the cell including chemical damage such as caused by free radicals, excitatory amino acids and amyloid plaque. For example, the above combination is more effective for neuroprotection than either anti-oxidant or polycyclic phenolic compound alone and therefore presents a novel therapeutic approach to treating neuron loss in human subjects that occurs in neuro-degenerative diseases such as Alzheimer's disease. In addition the combination therapy disclosed here has utility in treating other disease conditions which result from enhanced cell death including ischemia, trauma and aging.

Simpkins only provides data supporting the *combination* of (i) polycyclic phenols such as 17 β -estradiol, α -estradiol or estratriene-3-ol with the (ii) anti-oxidant glutathione (GSH). (See examples 1-3). No other combinations are tested or formulated.

Claim 1 was previously amended to specifically remove reference to kaempferol and quercetin. Claim 1 has now been further amended to remove reference to formula 'C' compounds which superficially resemble kaempferol and quercetin. The claim has also been amended to delete 'galangin', 'rhamnetin' and 'quercetagenin', compounds which superficially resemble those noted above.

Claim 1 of the pending application was previously amended to specifically remove reference to flavonoids by omitting formula 'C' (flavonoid backbone) and all individually listed compounds which resemble the flavonoids kaempferol and quercetin. This claim was further amended to remove all of the individually listed compounds. Therefore the scope of the claimed invention now encompasses compounds of formulas A, B and D does not encompass any compounds which are flavonoids. It is therefore difficult to understand the Examiners steadfast contention, as stated in the Office Action on page 3, that "*... the substitution of one flavanoid for another within the same genus would have been obvious to a person skilled in the art.*"

Applicants respectfully submit that as the instant claims exclude the entire genus of disputed compounds (flavonoids) that a finding of obviousness is incorrect.

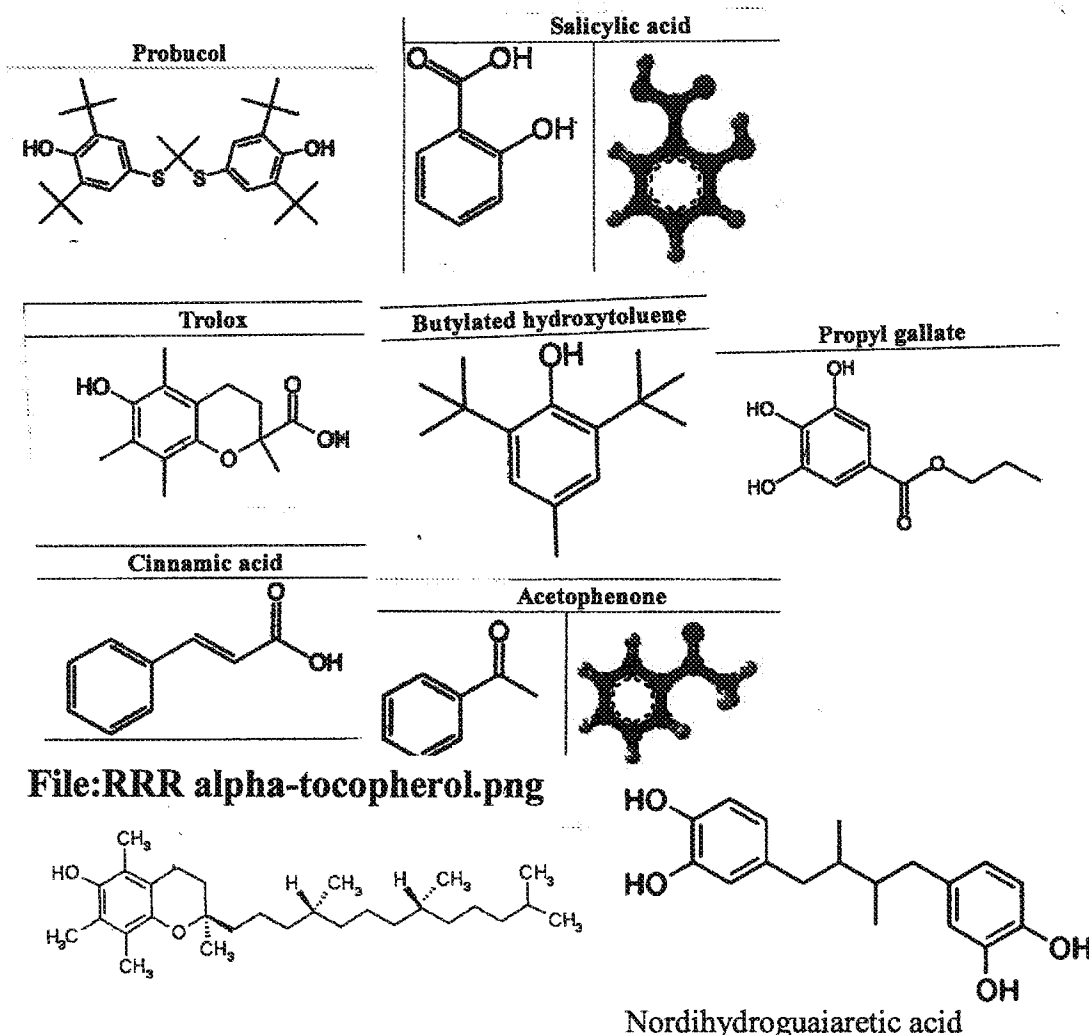
The Office Action dated 04/26/12 uses the term 'polyphenols' which is inaccurate in view of Simpkins since clear reference is made to two quite different types of phenolics. Simpkins first makes reference to 'polycyclic phenolics' used to describe the estrogens and estrogen like compounds. The second term 'phenols' is used by Simpkins to describe a subclass

of antioxidants. To best address the stated rejection Applicant has interpreted 'polyphenols' as used in the Office Action to encompass both types of compounds described by Simpkins.

Turning first to Simpkins' polycyclic phenolics, it is clear that the claimed invention in no way encompasses compounds related to estrogens or steroids. None of the claimed compounds possess the steroid backbone containing rings A-D as illustrated above. Although compounds of formula D of the claimed invention have a backbone which is four fused rings, the rings are fused in a different configuration from the polycyclic phenolics of Simpkins. Claimed Formula D compounds are comprised of four fused cyclohexanes, not three and additionally two of the rings possess a heteroatom. There are also two carbonyl groups on two of the rings which is different from the polycyclic phenolics of Simpkins. Applicant submits that the skilled person would readily appreciate that the polycyclic phenolics of Simpkins are not encompassed by the claimed invention and therefore a 'simple substitution' is not possible.

Simpkins teaches that one subclass of antioxidants could be phenols. Simpkins does not define phenols but it would be understood by the skilled person that phenols are compounds containing a six-membered aromatic hydrocarbon ring bonded directly to a hydroxyl group. The definition of 'phenol' in Wikipedia contains a link to 548 pages listing many different phenols. Each page of the 548 pages lists on average 132 compounds. The skilled person would appreciate that a total of over 72,000 different compounds can be considered to be phenols. A copy of the first 3 pages of the 548 pages of this definition is included in the appendix.

Simpkins teaches the following different classes of phenols which encompass many compounds as the phenol can be unsubstituted, mono-substituted, di-substituted and in one case tri-substituted.



Of the illustrated polyphenols, Simpkins tested only tocopherol which would lead the skilled person to conclude that the double ring and long chain hydrocarbon may be important structural features of a polyphenol that contribute to efficacy. In essence leading the skilled person away from the claimed invention. Although Simpkins teaches a trihydroxylated propyl gallate this is outside of the scope of the claimed invention as the claims do not permit that the X or R₁ substituents on formulas A or B can be esters. It would be appreciated by the skilled person that none of the phenols specifically disclosed by Simpkins fall within the scope of the claimed invention in contrast to what is incorrectly alleged in the Office Action.

Applicant submits that the skilled person would firstly not be motivated to conduct a simple substitution of one phenol for another as the category of phenols taught by Simpkins is very broad. Secondly the skilled person would have no reasonable expectation of success for phenols in general as only one was tested displaying moderate results.

In order to substitute one phenol for another the skilled person would initially be faced with the choice of one of the eight different classes of compounds which are taught for use as antioxidants. The antioxidants actually tested by Simpkins [column 9, table 1] further include compounds which are sugar acids, organic acids, organo-sulfur compounds and peptides. Only the peptide, glutathione (GSH), demonstrates decent results within the cited article suggesting its potential use as an antioxidant.

If the skilled person ignored the data and decided instead to proceed with a phenol they would be faced with a tremendously broad and varied group of compounds as discussed above. Simpkins only teaches the use of one phenol, tocopherol, as an antioxidant. Given the scarceness of direction regarding the choice of a phenol, the skilled person would be left with the overwhelming choice of over 72,000 phenols to select from in order to substitute one phenol for another as suggested by the Examiner. Testing the complete list of phenols for antioxidant activity according to the methods presented in Simpkins would indeed be an onerous affair requiring great expense and time. Each of the 72,000 phenols would require a preliminary dose response evaluation, the method of which was not disclosed in Simpkins, to narrow the dosage range to be tested in the assay. The laborious assay itself would then be needed to be conducted for each of the 72,000 different phenols. Therefore, Applicant submits that the skilled person would firstly not be motivated to conduct a simple substitution as no direction is provided by Simpkins which would help direct the skilled person to such a "simple substitution" and secondly the skilled person would have no reasonable expectation of success due to the overwhelming nature of the scope of experimentation required, nor would simply substituting any phenol from that vast genus yield predictable results.

The Applicant further submits that Simpkins has been mischaracterized which has led to incorrect allegation that the claimed invention encompasses the compounds taught by Simpkins.

2. Teachings of Snow *et al* as cited in the Office Action

The office action alleges that the prior art teaches species within the genus of the claimed compounds and their use for the treatment of Alzheimer's disease.

Applicants respectfully submit that (a) the instant claims do not encompass any of the compounds taught by Snow nor do they include similar polyphenols, and further that unlike the allegation in the Office Action (b) Snow does *not* teach that any actual compounds have amyloid inhibitory activity or have been used in the treatment of Alzheimer's. Snow only recites a list of desirable compounds. And finally (c) only plant extract fractions, containing an unknown mixture of compounds, all unidentified, display such activity.

The introduction and background of the Snow patent teach that extracts from the inner bark of *Uncaria tomentosa* have amyloid inhibitory activity (Column 2, lines 10-30). Applicant respectfully submits that Snow has been mischaracterized. Snow has not isolated or tested any specific compounds with definitive structures, and no individual compounds were shown to have activity nor was it demonstrated that compounds were used for the treatment of Alzheimer's.

The skilled person reading this patent would appreciate that while an extract of commercially available *Uncaria* inner bark was prepared; it was only an unpurified fraction of the extract that was shown to have activity. No individual compounds were isolated, identified or demonstrated to have activity. The inventory of compounds listed in columns 3-10 and cited in the Office Action is merely a wish list of desirous compounds that (a) Snow hopes to isolate from *Uncaria*, and (b) hopes that they can be shown to have activity. The skilled person in this instance is highly educated, holding at least a doctorate in chemistry, biochemistry or the pharmacological sciences and would not be at all swayed by the teachings of Snow since there is no evidence which supports that even a single defined compound actually possess activity.

All of the compounds cited in the Office Action are wished for and ultimately it was never shown that *Uncaria* possess any of the wished for compounds and it is never stated, nor have references or data been supplied that support that the wished for compounds have amyloid inhibitory activity as none were ever tested.

Snow, at column 3, lines 12-32 recites a list of phytochemicals about which it is stated are "contained within *Uncaria*" and it is an object of the invention to use (future tense) these compounds for the treatment of amyloid. The paragraph which precedes the list of constituents begins with the phrase; "These constituents are *believed* to include....". The skilled person

without supporting proof would (a) not accept that these phytochemicals are actually present in *Uncaria* and (b) that such constituents would be useful for the treatment of amyloid.

Column 7, lines 25-57 is yet another shopping list of hoped for compounds that the authors of this patent would like to see have amyloid inhibitory activity. Broadly several classes of compounds are listed: (1) oxindole alkaloids, (2) quinovic acid glycosides, (3) proanthocyanidins, (4) polyphenols, (5) triterpines and (6) plant sterols followed by a more specific list of hoped for candidates. The skilled person would understand that five of the six classes do not relate in any way to the claimed compounds (please see the attached Wikipedia excerpts in the appendix for definitions). The remaining category - polyphenols appears to be the class of compounds on which the rejection appears based. In terms of examples, only two somewhat similar polyphenols are listed in Snow keeping in mind neither were tested nor stated explicitly to have activity. However, neither compound falls within the scope of the claims and for further clarity, claims 1 and 18 have been amended.

Finally, the compounds in column 9, lines 50 to column 10, line 15 are merely reiterations of the aforementioned compounds.

In conclusion Applicant submits that Snow has been mischaracterized as no individual compounds were isolated, identified or demonstrated to have activity. In view of this lack of direction, the skilled person would neither be motivated to consider the shopping list of compounds for which no efficacy is taught, nor would they have a reasonable expectation of success when trying to select one of a possible collection of 72,000 different phenols, nor would such results be predictable. Therefore, Applicant submits that the skilled person would not be motivated to conduct a simple substitution in view of the teachings of Snow.

3. Teachings of Simpkins combined with Snow

Taken together, Simpkins and Snow do not provide any recognizable direction to the skilled person that would lead them a selection of suitable compounds from the many thousands of chemicals known as polyphenols. Neither Simpkins, nor Snow on their own suggest to the skilled person which polyphenol or flavanoid might have suitable structural characteristics to which any such efficacy can be attributed. It is in the void of suggestion that the skilled person would lack the motivation to combine these references and furthermore lack a reasonable

expectation of success due to an absurd amount of experimentation that would be required all based on the uncorroborated and perhaps unsubstantiated statements made in Snow .

Finally, MPEP § 2143 states that “[t]he key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit” (emphasis added). According to MPEP § 2143, rationales that may support a conclusion of obviousness include the simple substitution of one known element for another to obtain predictable results. MPEP also requires that some rationale be provided in order to support a conclusion of obviousness. In this case, the Office Action has failed to present any type of rationale other than the allegation that a simple substitution would be obvious to the skilled person. In particular, the rejection lacks a clear articulation of the reasons why such a substitution would allegedly have been obvious especially in view of the lack of actually teachings in the cited art. Therefore, the rejection cannot be supported per the requirements set forth by the United States Supreme Court in the *KSR* decision. Thus, it is respectfully submitted that the rejection is improper and must be dismissed.

Applicant also is unclear as to why the Office Action makes reference to a previous response to office action which contained a different set of the claims which are no longer on file. Applicant respectfully submits that the claims currently on file must be examined on their merits and that to consider previous iterations of the claims to support the current rejection is improper and has no legal basis.

Applicant believes they have responded fully to all of the concerns expressed in the Office Action. In light of the above remarks, the Applicant respectfully requests that the Examiner reconsider this application with a view towards allowance. Please apply any charges, or any credits, to Deposit Account 50-4423. If the Examiner has any further concerns, Applicant requests an immediate call at the telephone number below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Rebecca Eagen', written over a horizontal line.

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